SPONTANEOUS INTRACEREBRAL HEMORRHAGE. HYPERGLICEMIA AND BRAIN PERFUSION SPECT

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ABSTRACT

Despite progression in medical science, intracerebral hemorrhage is the deadliest and least treatable form of stroke. Most of data about pathophysiology of ICH are obtained from animal models. Some of these models are able to reproduce human ICH with high accuracy, but most of them determine artificial changes in brain. Among the human in vivo research tools we can name Nuclear Medicine imaging – PET-CT and SPECT with HMPAO or ECD-99mTc. The aim of our study was to report the pattern of cerebral perfusion in patient with acute stage of ICH and its relation with hematoma localization, presence of risk factors and CT scan findings.

INTRODUCTION

Despite progression in medical science, intracerebral hemorrhage is the deadliest and least treatable form of stroke.

Intracerebral hemorrhage occurs in approximately 10 -15% of all stroke (1,2,3) and has a higher incidence in populations with a high incidence of untreated essential hypertension

Despite the progress of multimodality imaging, in vivo research modalities are very limited, and most of data about pathophysiology of ICH are obtained from animal models. Some of these models are able to reproduce human ICH with high accuracy, but most of them determine artificial changes in brain.

Among the human in vivo research tools we can name the MRI with its newly developed functional techniques, and Nuclear Medicine – which usually is limited because of the high cost and complicate procedure for authorizing of newly developed radiopharmaceuticals. However, there are several techniques already available which can be used for in vivo evaluation of ICH patients – cerebral SPECT with HMPAO or ECD, PET-CT, but large, randomized studies on functional nuclear imaging have not been carried out.

Some studies reported the role of SPECT and PET in the assessment and predicting outcome of patients with stroke. The great majority of these studies are carried out in patients with cerebral infarction (4,5,6). Those performed in ICH patients – very few and with a very limited no of patients included – all reported some common findings, such as perihematomal hypoperfusion, adiacent hyperperfusion, presence of hypoperfused areas distant from hematoma, or cerebellar diaschisis. These changes are, in some studies, correlated with the outcome, but none correlated these findings with other predictors of outcome (7,8,9,10).

AIM

In this study we report the pattern of cerebral perfusion in patient with acute stage of ICH and its relation with hematoma localization, presence of risk factors and CT scan findings.

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Table 1

Hematoma localization	putaminal	talamic	lobar	caudat	total
No.	9	8	6	3	26
age (y)	39-72 (m=56,7)	41-70 (m=55.37)	38-72 (m=55)	47-58 (m=53,6)	38-72 (m=55,68)
sex (m/f ratio)	5m/4f (1.25)	6m/2f (3)	4m/2f (2)	2m/1f (0.5)	16m/10f(1.6)

METHOD

We performed brain perfusion SPECT with 99mTc- HMPAO in 26 patients with CT proven ICH. Patients` age was between 38 and 72 years, (mean 55.57). 17 of them were male. Demographic characteristics of patients are shown in table 1.

All patients had clinical and biological evaluation at presentation (within the first 8 h from stroke onset), and all were assessed for the presence/absence of risk factors – known hypertension, diabetes, smoking, dislipidemia, obesity.

All patients undergone CT scan on admission and diagnosis of ICH confirmed.

SPECT

The radiotracer used for SPECT imaging was 99mTc-HMPAO. HMPAO (hexametil-propilenamin-oxime) is a molecule which normally diffuses through the blood-brain barrier; it accumulates in the brain through its intracellular conversion from a lipophilic to a hydrophilic form within the brain parenchyma (11)

Acquisition of SPECT images was made 30 min after iv inj of 25 mCi of 99mTcHMPAO, using a dual head gamma camera Philips Axis with a low energy, high resolution collimator. We acquired 64 projections, with 40s for each projection, and the matrix size 128x128. Transaxial sections were then reconstructed using filtered backprojection (Butterworth filter). Axial sections were obtained parallel to orbitomeatal line. Coronal and sagittal images were then reconstructed.

In all patients we visually compared the images with the CT scan, performed in the same day with brain SPECT. We assessed and reported our results after analyzing the diameter of perfusion defect on both scans and by means of the presence/absence of perfusion changes in the cerebral tissue adjacent to the hematoma and at distanced areas.

SPECT data were correlated with the CT findings – hematoma volume and location and with the data obtained from the patient records: age, sex, MAP, blood glucose level, presence of risk behavioral factors such as smoke and alcohol consumption

STATISTICAL ANALYSIS

All data were compared using the Student's t-test or the Mann-Whitney U test for continuous variables which were expressed as mean (SD); we used the chi -square ($\chi 2$) test (with Yate's correction when necessary) for categorical variables; presence of surrounding hypoperfused area was noted with 1, absence with 2 Statistical significance was set at $p < 0.05$ for a confidence interval of 95%.

RESULTS

Demographic characteristics of patients are shown in Table 1, in correlation with hematoma localization. No differences were observed in age distribution of different location. A slight reduced aged compared to the mean of the entire group seems to be in the caudate location. We noticed a male predominance in all subgroups.

In 21 patients (80.76%) perfusion defect corresponding to hematoma was greater than expected after CT scan. In 4 patients hematoma maximum diameter was comparable on CT and on SPECT images; in 1 patient with intraventricular hemorrhage we found a quasinormal aspect of the perfusion study (Figure 1).

In the group of patients with larger perfusion defect, SPECT revealed a large cold spot with a similar size compared with CT and a surrounding hypoperfused area (Figure 2,3).

We correlate the presence of hypoperfusion surrounding hematoma with demographic data and risk factors. We found no association between presence/absence of surrounding hypoperfusion and age or sex, and no association with alcohol consumption, dislipidemia or smoking. We found a

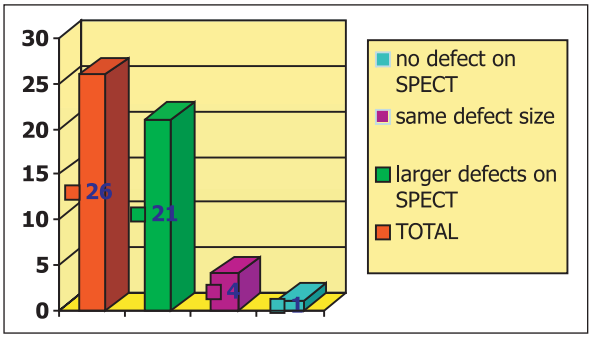

Figure 1. *Most of our patients (82.35%) shown a larger defect size on SPECT than expected after CT*

sis(12,13,14), but most authors agrees that the decreased level of perfusion and of CBF correlates with short term and long term outcome (6-10, 15)

Diabetes mellitus (DM) is currently considered by most authors a risk factor by far more important for ischemic rather than for haemorrhagic stroke (15, 16, 17). Some authors reported DM to be a significant risk factor for ICH (18, 19, 20) Despite of this apparent contradiction in demonstrating the potential of DM to be a risk factor for ICH, an increased number of researchers shown that when

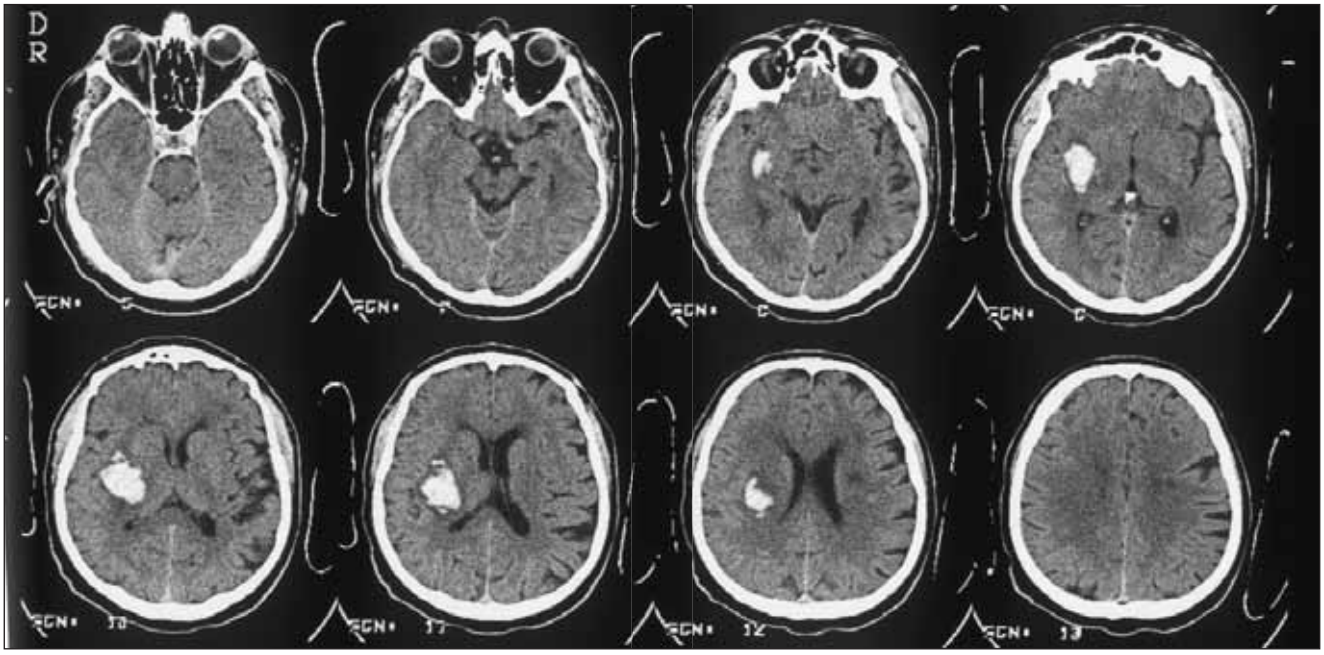

Figure 2. *CT scan – area with hematic density in right putamen, external capsule and corona radiata; small area of surrounding perilesional oedema.*

positive correlation between admission glucose level and presence of perihematomal hypoperfusion, with a significant difference between the mean glucose level ($p<0.05$) – Figure 4.

DISCUSSIONS

During the past years many experimental models and several human studies demonstrated a zone of perilesional reduction in blood flow around ICH and suggested the potential for perfusion recovery in these areas. Most of these studies support the theory of a decreased CBF adjacent to the hematoma, and some of them gave evidence of histological ischemic changes in perihematomal brain tissue. Several authors have suggested that perilesional hypoperfusion occurs without ischemia as a result of reduced metabolic demand or diaschi-

present, premorbid DM or high admission blood glucose levels have an important negative role on prognostic and mortality of these patients, comparative to those without DM, or to those with low admission blood glucose level (21-26). In a study published in 2005, R Fogelholm et al concluded that admission high blood glucose is a predictor for an increased 28-day case-fatality rate both in non-diabetic and in diabetic patients with ICH (27)

In our study, the mean admission blood glucose level was statistically significantly higher in patients with surrounding hypoperfusion. We suggest that this phenomenon can be explained by microangiopathic involvement of cerebral vessels related to hyperglycemia and diabetes mellitus and by alterations in blood-brain barrier structure and function.

Factors currently involved as cause of endothelial damage associated to hyperglicemia is oxida-

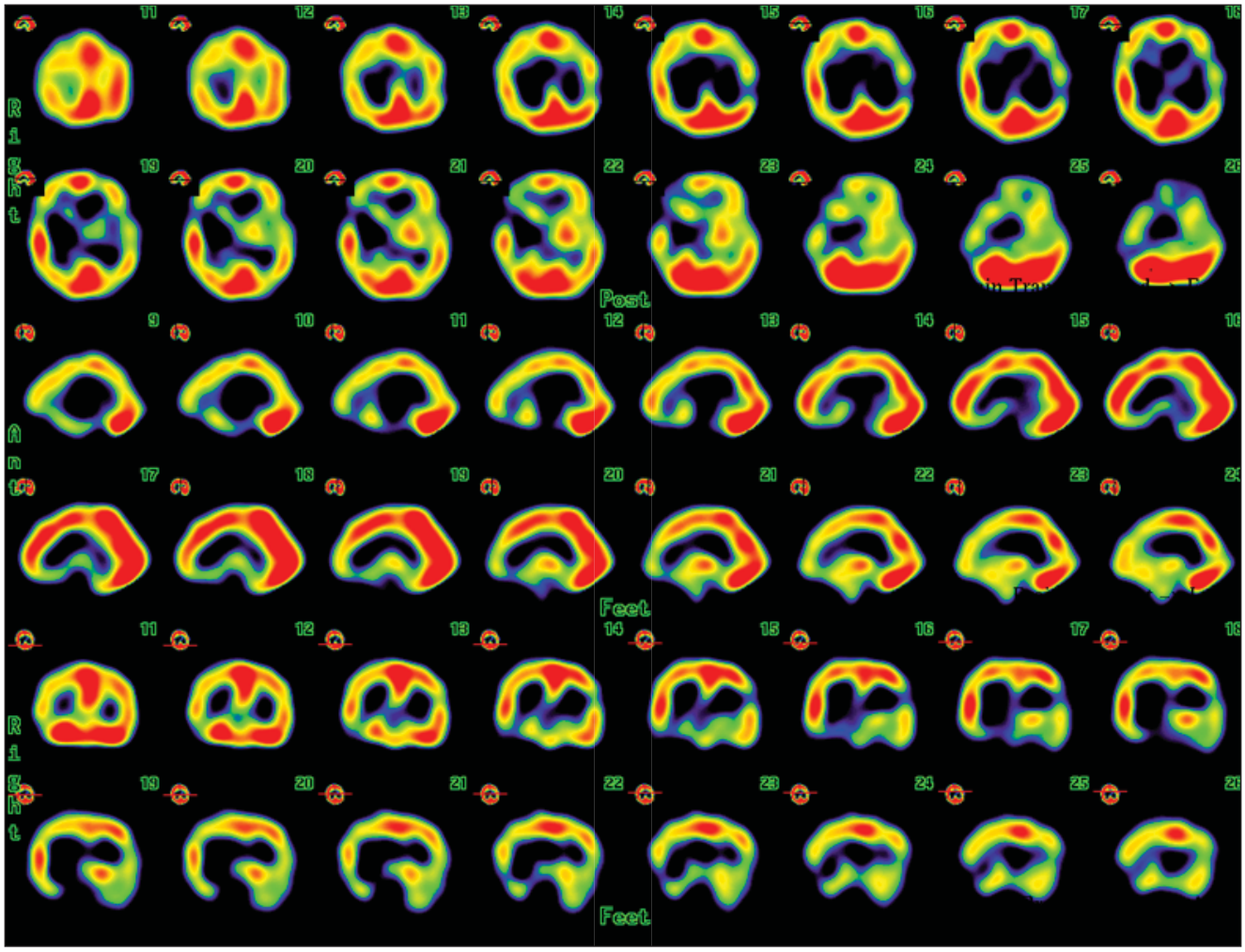

Figure 3. *Cold spot in right thalamus, corresponding to the hematoma. Reduced uptake of radiotracer in the basal nucleus, dorsolateral cortex and temporal.*

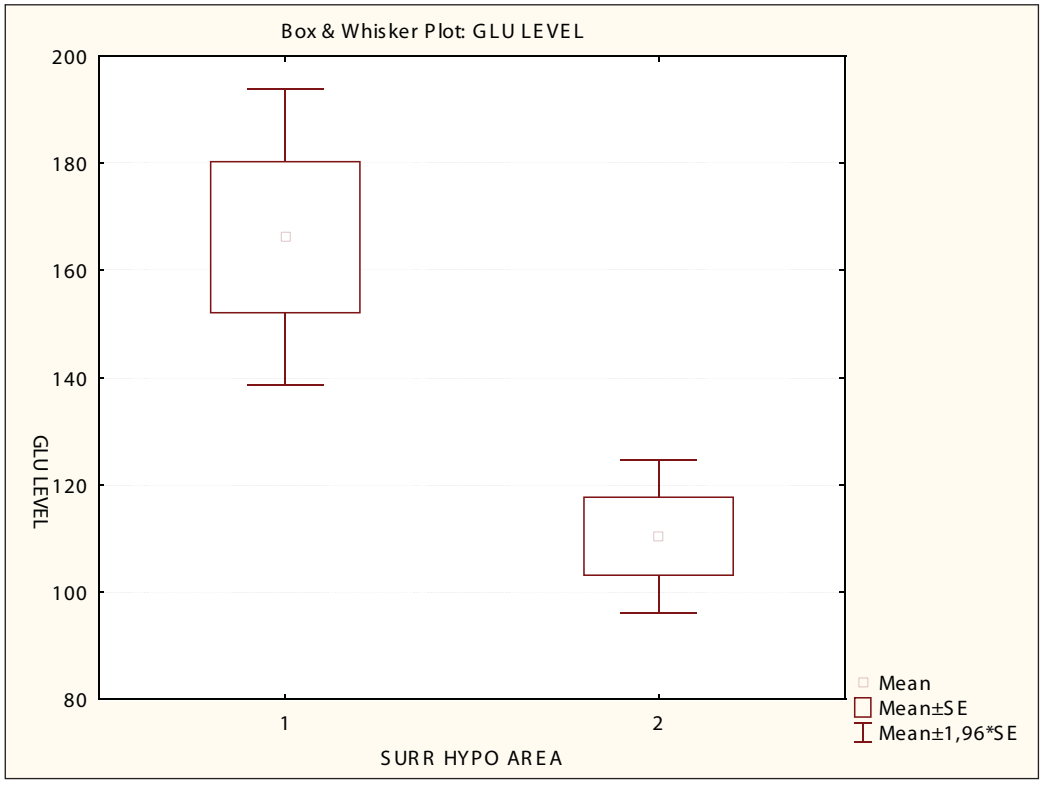

Figure 4. *Mean glucose level in patients that did show (1) and did not show (2) surrounding hypoperfused area on SPECT images; the difference between the two groups was significant ($p<0.05$)*

tive stress with subsidiary inflammation, leukocyte adhesion, and altered coagulation. Camera et al suggested that adhesion molecules could be considered as marker of endothelial damage and a potential therapeutic target (28)

Some authors consider that in ICH high level of blood glucose in acute stroke can be considered a stress reaction (24,29) or an expression of coexisting and premorbid diabetic glucose metabolism (30,31). In recent years, the amount of evidence which support the stress hypothesis of poststroke hyperglycemia is increasing. AHA guidelines for early management of ischemic stroke (2003) recommend control of hypoglycemia or hyperglycemia after stroke(32) and states that markedly elevated glucose levels should be lowered to <300 mg/dL (<16.63 mmol/L). At present there is no agreement on more aggressive lowering of hyperglycemia in acute stroke and results of currently performed randomized trials are waited.

CONCLUSIONS

In our SPECT study we found perfusion defect surrounding the hematoma area in a high percent of patients (80.76%!), with a significant higher admission blood glucose level compared to patients in which SPECT did not demonstrated perihematoma hypoperfusion. This area of surrounding hypoperfusion may contain viable cerebral tissue which can be a target for neuroprotective therapeutic strategies. Further studies are definitely needed in order to clarify if aggressive lowering the level of blood glucose has an impact on short term and long term outcome of ICH patients

Cerebral perfusion SPECT can be a very useful tool in assessment of patients with hemorrhagic stroke and for understanding the pathology of this serious disease. Further studies with larger number of patients are definitely required.

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